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Remarks

Claims 15-17 and 21-38 are pending in the application. Claims 1-14 and 16-22 were rejected. Claim 15 was objected to, for depending on a rejected claim. Claims 1-14 and 18-20 have been canceled. Claims 16, 17 and 21 have been amended. Claims 23-38 are new. Support for the claim amendments and additions can be found throughout the application, including the originally-filed claims. Importantly, no new matter has been added to the claims. The amendments to the claims should not be construed to be an acquiescence to any of the rejections. Rather, the amendments to the claims are being made solely to expedite the prosecution of the above-identified application. The Applicant reserves the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 USC § 120.

Claim Rejections - 35 USC § 103(a)

Reed et al. (US 5,746,997)

Claims 1-6, 8-12, and 16-19 are rejected as being unpatentable over Reed *et al.* (US 5,746,997). The Examiner contends that Reed teaches that any of the R₁ substituents (of formula 5 in column 5 of said reference) can be an alkyl chain of up to 10 carbons which the Examiner feels would be within the scope of a “polymer,” given its broadest reasonable interpretation. The Applicants respectfully traverse.

The Applicants submit that polymer, as understood by one skilled in the art, is:

any relatively high molecular weight molecule, the structure of which comprises the multiple repetition of units derived, actually or conceptually, from molecules of low relative molecular mass (specification, page 6).

Applying this definition to the Examiner’s assertion, one must conclude that the Examiner is considering the methylene unit as a monomer. Further, it would seem by this definition that *all* compounds should therefore be classified as polymers or co-polymers as they all consist of different monomers, such as methylenes, connected together. Polymers, as the definition provided in the specification asserts, must also be of high molecular weight. While “high” molecular weight is a qualitative description, the Applicants believe that one versed in the

art would not consider a ten-carbon fragment to be of high molecular weight. In short, the Applicant's assert that the classification of C₁₀ alkyl as a polymer is incorrect.

As the Reed patent does not disclose the use of polymers, and therefore does not teach all the limitations of the rejected claims, the Applicant's respectfully submit that Reed does not render unpatentable the rejected claims. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the rejections of said claims under 35 U.S.C. § 103(a).

Reed et al. (US 5,746,997) in view of Wilbur (US 5,609,848)

Claim 7 is rejected as being unpatentable over Reed *et al.* (US 5,746,997) in view of Wilbur *et al.* (US 5,609,848). The Examiner contends that Wilbur teaches methods involving Sn-substitution of aryl compounds to provide diagnostic or therapeutic agents. However, as explained above, Reed does not teach the use of polymers. Because Wilbur likewise does not teach polymers, the combination of Reed with Wilbur still fails to teach all of the limitations of the rejected claims. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the rejections of claim 7 under 35 U.S.C. § 103(a).

Hunter et al. (WO 99/18053) in view of Reed (US 5,746,997) & Wilbur (US 5,609,848)

Compound Claims 1-14

Compound claims 1-14 are rejected as being unpatentable over Hunter *et al.* (WO 99/18053) in view of Reed (US 5,746,997) and Wilbur (US 5,609,848). The Examiner explains that, in his opinion, the only difference between Hunter and the instant application is that "Hunter does not disclose that the aryl group may be a polycyclic or heterocyclic aryl." The Examiner goes on to state that Wilbur teaches the equivalence of benzene to polycyclic aryls, or heterocyclic aryls, in analogous precursor compounds.

Claims 1-14 have been canceled. The cancellation of the claims is being made solely to expedite the prosecution of the above-identified application. The Applicant expressly reserves the option to prosecute further the same or similar claims in subsequent patent applications entitled to the priority date of the instant application.

Method Claims 16-22

In addition, method claims 16-22 were rejected as being unpatentable over Hunter *et al.* (WO 99/18053) in view of Reed (US 5,746,997) and Wilbur (US 5,609,848) for the reasons explained above. The Applicants respectfully traverse.

The Applicants assert the existence of important distinctions between the chemistry of benzene and polycyclic aromatic or heterocyclic aryl compounds. For one, polycyclic aromatic and heterocyclic aryl compounds are often more electron-rich, as compared to a phenyl ring, making their corresponding aldehydes difficult to oxidize. This effect was systematically investigated by Mitamura and co-workers in 1988 (*Bull. Chem. Soc. Jpn.* 1988, 61, 4464) (copy provided). The Mitamura reference establishes that when hydrogen peroxide is used as an oxidant in the oxidation of polycyclic aromatic aldehydes or heterocyclic aryl aldehydes, phenols, *not acids*, are isolated. As Hunter teaches only the use of hydrogen peroxide, the application of the methods in Hunter would not have led to the desired compound. Reed and Wilbur do not supply this missing claim limitation. Therefore, Hunter in view of Reed and Wilbur does not teach every limitation of claims 16-22 as required for a *prima facie* showing of obviousness under 35 U.S.C. § 103(a).

To emphasize the importance of the choice of oxidant, and in order to expedite prosecution, the Applicant has amended claims 16 and 21 to encompass a specific set of oxidants, excluding hydrogen peroxide. Support for this Markush group can be found through out the specification, for example in the claims and on page 42 (¶2). Therefore, no new matter has been added. The Applicant's respectfully submit that Hunter in combination with Wilbur and Reed does not render unpatentable the amended claims. Therefore, the Applicants respectfully request reconsideration and withdrawal of the rejections of claims 16, 17, 21 and 22 under 35 U.S.C. § 103(a).

As made necessary by the cancellations described above, claim 16 has been rewritten so as not to depend on canceled claims 1-14, and claims 23-37 have been added, to capture subject matter originally encompassed by claim 16. In addition, in the interest of clarity, claims 16 and 21 have both been amended to contain a Markush group of radioisotopes. Support for the Markush groups can be found through out the specification, for example on pages 7 (¶3) and 43

(¶6). Please note that Claim 16 has also been slightly amended to establish proper antecedent basis, removing the ambiguity caused by the repetition of the term “radioactive compound”. Similarly, claims 17 and 21 have been amended to adhere to the rules of proper claim mechanics. Lastly, solely in order to expedite prosecution, the applicant has chosen to cancel all “kit” claims (*i.e.*, claims 18-20).

Allowable Subject Matter

Claim 15 is objected to as being dependent upon a rejected base claim. The Examiner explains that this claim would be allowable if rewritten in independent form. Claim 15 as previously presented is in independent form and thus the Applicants request that Examiner lift the objection to claim 15 and that this claim be allowed.

Conclusion


In view of the above amendments and remarks, the Applicants believe that the pending claims are in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite prosecution of the application, the Examiner is urged to contact the undersigned.

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The Baeyer-Villiger Reaction of Polycyclic Aromatic Aldehydes: Preparation of Polycyclic Phenols

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Synopsis. Baeyer-Villiger reactions of such polycyclic aromatic aldehydes as 2-dibenzofurancarbaldehyde with various peroxy compounds have been studied in detail, giving predominantly the corresponding phenols.

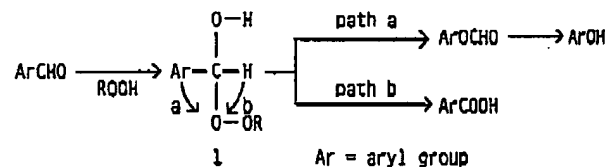
In contrast to simple benzenoid aromatics, only a little attention has been paid to such polycyclic aromatic compounds as naphthalene, dibenzofuran, anthracene and so on, though they have attractive attributes, i.e., their rigid ring skeletons and rich π -electron systems. We have been interested in the reaction characteristic of the polycyclic aromatic systems to provide a variety of useful derivatives. In this paper, we wish to report on the Baeyer-Villiger reaction (B-V reaction)¹⁾ of polycyclic aromatic aldehydes yielding a series of polycyclic phenols.

Several kinds of polycyclic aromatic aldehydes²⁾ were allowed to react with *m*-chloroperbenzoic acid (MCPBA) in dry dichloromethane at room temperature under an argon atmosphere. The results are shown in Table 1. Polycyclic aromatic aldehydes gave the corresponding phenols predominantly, while benzaldehyde yielded a mixture of phenol and benzoic acid. This difference can be attributed to a difference in the electron-donative nature between the polycyclic aromatic ring and the benzene ring. The mechanism shown in Scheme 1 is generally proposed.³⁾ A peroxy compound (ROOH) attacks the carbonyl group of an aldehyde (ArCHO) to afford an intermediate 1, followed by a migration of the aryl group, Ar, (path a) or the hydride, H, (path b). The relative migratory aptitude of Ar and H depends on their electron-donative nature, so that the more electron-donative polycyclic aromatic ring migrates predominantly to give the formate, which is transformed into the phenol, ArOH, by alkaline hydrolysis. Thus, this work presents a new synthetic method regarding polycyclic phenols.

Table 1. B-V Reaction of Polycyclic Aromatic Aldehydes with MCPBA

| Run No. | Ar | X ^{a)} % | Yield/% | |
|---------|----|----------------------|---------|--------|
| | | | ArOH | ArCOOH |
| 1 | | 81 | 32 | 42 |
| 2 | | 95 | 80 | 2 |
| 3 | | 75 | 48 | 16 |
| 4 | | 97 | 79 | 2 |
| 5 | | 94 | 85 | 2 |
| 6 | | 97 | 86 | 1 |
| 7 | | 99 | 92 | 2 |

a) X is the conversion of the aldehyde.



Scheme 1.

Many kinds of peroxy compounds were examined as oxidants instead of MCPBA in this B-V reaction of 2-dibenzofurancarbaldehyde (2). Table 2 shows the results of a reaction of 2 with aqueous hydrogen peroxide (30 wt%) in the presence of various acids to yield 2-dibenzofuranol (3) and 2-dibenzofurancarboxylic acid (4). The reaction was strongly affected by the

Table 2. B-V Reaction of 2 with Aqueous Hydrogen Peroxide

| Run No. | H ₂ O ₂ /2 mol/mol | Solvent | T ^{a)} °C | t ^{b)} h | X ^{c)} % | Yield/% | |
|---------|---|--|-----------------------|----------------------|----------------------|---------|----|
| | | | | | | 3 | 4 |
| 8 | 2.0 | CH ₃ COOH | 40 | 168 | 50 | 2 | 47 |
| 9 | 1.3 | HCOOH | 20 | 20 | 98 | 76 | 3 |
| 10 | 1.0 | HCOOH | 20 | 20 | 95 | 81 | 1 |
| 11 | 1.2 | CF ₃ COOH | 20 | 20 | 85 | 13 | 1 |
| 12 | 1.2 | CH ₃ COOH-H ₂ SO ₄ (5%) ^{d)} | 40 | 24 | 86 | 49 | 4 |
| 13 | 1.1 | CH ₃ COOH-CH ₂ ClCOOH (5%) ^{d)} | 40 | 20 | 80 | 66 | 7 |
| 14 | 1.2 | CH ₃ COOH-CF ₃ COOH (5%) ^{d)} | 40 | 20 | 60 | 34 | 13 |
| 15 | 2.0 | CH ₃ OH-HCOOH (30%) ^{d)} | 40 | 24 | 41 | 2 | 22 |
| 16 | 1.2 | CH ₃ OH-H ₂ SO ₄ (5%) ^{d)} | 40 | 48 | 100 | 36 | 64 |
| 17 | 1.3 | (CH ₃) ₂ CO-H ₂ SO ₄ (5%) ^{d)} | 40 | 24 | 78 | 1 | 55 |

a) T is the reaction temperature. b) t is the reaction time. c) X is the conversion of 2. d) The concentration of the second material.

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Table 3. B-V Reaction of 2 with Various Peroxy Compounds

| Run No. | Peroxy Compound ^{a)} | Solvent | T °C | t h | X % | Yield/% | |
|---------|---|---|---------|--------|--------|---------|-----|
| | | | | | | 3 | 4 |
| 18 | <i>t</i> -BuOOH | HCOOH | 40 | 48 | 11 | 3 | 0.2 |
| 19 | <i>t</i> -BuOOH | CH ₃ OH-H ₂ SO ₄ ^{b)} | 40 | 48 | 90 | 61 | 15 |
| 20 | <i>t</i> -BuOO-COCH ₃ | CH ₃ OH-H ₂ SO ₄ ^{b)} | 40 | 24 | 43 | 29 | 9 |
| 21 | $\begin{array}{c} \text{CH}_3 \\ \\ \text{t-BuOO}-\text{C}-\text{OO}-\text{t-Bu} \\ \\ \text{CH}_3 \end{array}$ | CH ₃ OH-H ₂ SO ₄ ^{b)} | 40 | 24 | 52 | 17 | 17 |
| 22 | (PhCO) ₂ O ₂ | CH ₃ OH-H ₂ SO ₄ ^{b)} | 40 | 48 | 92 | — | 85 |
| 23 | K ₂ S ₂ O ₈ | CH ₃ OH-H ₂ SO ₄ ^{b)} | 40 | 24 | 56 | 9 | 29 |
| 24 | CH ₃ CO ₃ H | (CH ₃ CO) ₂ O | 40 | 24 | 97 | 2 | 68 |

a) The molar ratio of the peroxy compound to 2 is 1.2. b) The concentration of H₂SO₄ is 5 wt%.

acidity of the acid used. The reaction in formic acid gave 3 in high yield (81%, Run 10) and high selectivity, while the reaction in acetic acid proceeded slowly and gave 4 (47%, Run 8). When the reaction was carried out in trifluoroacetic acid, the yield of 3 was low (13%) and tarry materials were obtained (Run 11). Acid catalysts yield the conjugate acids of aldehydes and accelerate the nucleophilic additions of peroxides to the protonated carbonyl groups (Scheme 1).³⁾ The acidity of formic acid ($pK_a=3.75$ at 25 °C) is stronger than that of acetic acid ($pK_a=4.76$); thus, a reaction in formic acid gives 3 predominantly. In the case of trifluoroacetic acid ($pK_a=0.23$), its acidity is so strong that 2 and products would be further converted to tarry materials. When sulfuric acid ($pK_a=1.99$, Run 12) or chloroacetic acid ($pK_a=2.87$, Run 13) was added to acetic acid solvent, the yield of 3 increased, while the addition of formic acid or sulfuric acid in methanol (Runs 15, 16) and acetone (Run 17) did not improve the yield of 3.

Table 3 shows the results of a reaction of 2 with several kinds of peroxy compounds. The reaction of 2 with *t*-butyl hydroperoxide (*t*-BuOOH) in methanol-sulfuric acid (Run 19) proceeded more rapidly and gave 3 more dominantly than that in formic acid (Run 18). When *t*-butyl peracetate (Run 20) and 2,2-bis(*t*-butyldioxy)propane (Run 21) were used as oxidants, 3 was also obtained more than 4. On the other hand, other peroxy compounds such as dibenzoyl peroxide (Run 22), potassium peroxodisulfate (Run 23) and peracetic acid (Run 24) gave 4 predominantly. These results indicate that the nature of the leaving group of the intermediate 1 may affect the relative migratory tendency of the aryl and the hydride groups.

To sum up, polycyclic phenols were obtained from the corresponding aldehydes under the system of MCPBA-CH₂Cl₂, H₂O₂-HCOOH, H₂O₂-CH₃COOH-CH₂ClCOOH or *t*-BuOOH-CH₃OH-H₂SO₄. This reaction provides a new method for the preparation of polycyclic phenols.

Experimental

All melting points were measured by a Yanagimoto micro melting point apparatus and were uncorrected. NMR spectra were taken on a JEOL JMN-FX90 spectrometer. Mass spectra were obtained with a Shimadzu QP-1000 spectrome-

ter. Gas chromatographs were obtained with a Shimadzu GC-9A. All aldehydes, except for 2, were commercially available and purified by a column chromatography on silica gel with dichloromethane as the eluent. Solvents such as benzene and dichloromethane were dried on Molecular Sieves 3A. All peroxy compounds and acids, except for peracetic acid, were purchased commercially and were used without purification. Peracetic acid was prepared in situ by the reaction of acetic anhydride with aqueous hydrogen peroxide.⁴⁾

Preparation of 2-Dibenzofurancarbaldehyde (2). To a solution of 21.4 g (127 mmol) of dibenzofuran in 40 cm³ of dry benzene was added 38.3 g (287 mmol) of aluminum chloride and 1.2 g (12 mmol) of copper(I) chloride in a 200 cm³ autoclave. It was filled with carbon monoxide until the pressure reached 4.9 MPa; the mixture was then stirred at 40 °C for 3 h maintaining the pressure at 4.9 MPa. The mixture was poured onto 500 g of ice to hydrolyze the complex of the product and aluminum chloride. The aqueous layer was removed; then, the organic layer was washed with 100 cm³ of water and dried (magnesium sulfate). After evaporation in vacuo, the residue was purified by a column chromatography (silica gel, dichloromethane). The eluent was evaporated, and the residual solid was recrystallized from petroleum ether to afford 17.4 g of 2 (70% yield).

2-Dibenzofurancarbaldehyde (2): Mp 61–63 °C; ¹H NMR (CDCl₃) $\delta=7.1$ – 7.4 (4H, m), 7.6 – 7.8 (2H, m), 8.09 (1H, d, $J=2$ Hz) and 9.90 (1H, s, CHO); ¹³C NMR (CDCl₃) $\delta=111.71$, 111.81, 120.75, 122.54, 123.14, 123.30, 124.71, 127.96, 128.66, 131.91, 156.62, 159.27, and 190.69; MS (70 eV) m/z (rel intensity) 196 (M^+ ; 90), 195 (100), 167 (30), and 139 (58); Found: C, 79.62; H, 4.08%; Calcd for C₁₃H₈O₂: C, 79.61; H, 4.08%.

B-V Reaction of 2 with MCPBA. To a solution of 392 mg (2 mmol) of 2 in 5 cm³ of dry dichloromethane was added 414 mg (2.4 mmol) of MCPBA. The mixture was stirred at room temperature under an argon atmosphere for 20 h. An excessive amount of aqueous sodium thiosulfate solution was added to the reaction mixture and no remains of MCPBA were checked by potassium iodide-starch paper. After an addition of 10 cm³ of 2 moldm⁻³ NaOH and 10 cm³ of methanol, the mixture was stirred for 0.5 h and neutralized to pH 7–8 with 1 moldm⁻³ HCl and aqueous sodium hydrogencarbonate solution, then extracted with 30 cm³ of dichloromethane. The amounts of 2 and 3 in the organic layer were determined by gas chromatography (200 °C, Fuloxylate-K, 3 mm \times 2 m) using dimethyl 2,6-naphthalenedicarboxylate as an internal standard. After the organic layer was evaporated, 3 was isolated from the residue by column chromatography (silica gel, dichloromethane) and recrystallization from ethanol.

2-Dibenzofuranol (3): Mp 136–137 °C; $^1\text{H NMR}$ (CDCl_3) δ =4.82 (1H, s, OH), 6.95 (1H, dd, J =9 Hz, 3 Hz), 7.1–7.7 (5H, m), and 7.90 (1H, dd, J =9 Hz, 2 Hz); MS (70 eV) m/z (rel intensity) 184 (M^+ ; 100), 155 (9), 128 (17), and 127 (10); Found: C, 78.07; H, 4.35%; Calcd for $\text{C}_{12}\text{H}_8\text{O}_2$: C, 78.28, H, 4.34%.

The aqueous layer, which contained 4, was acidified with concentrated HCl and extracted with 30 cm³ of ethyl acetate. A diazomethane-ether solution was added to the organic layer to convert 4 into the methyl ester; then, the amount of the methyl ester was measured by gas chromatography. The methyl ester was isolated by column chromatography (silica gel, dichloromethane).

Methyl 2-Dibenzofurancarboxylate: $^1\text{H NMR}$ (CDCl_3) δ =3.97 (3H, s), 7.3–7.7 (4H, m), 7.9–8.2 (3H, m), and 8.60 (1H, d, J =2 Hz); MS (70 eV) m/z (rel intensity) 226 (M^+ ; 66), 195 (100), 167 (25), and 139 (31); Found: C, 74.30; H, 4.48%; Calcd for $\text{C}_{14}\text{H}_{10}\text{O}_3$: C, 74.33; H, 4.46%.

The products of the B-V reaction of other aldehydes (Table 1) were analyzed using the same method, except for the reaction of 9-anthracenecarbaldehyde. They were identified through a comparison of their respective retention times in gas chromatography and the mass spectra with those of commercially available chemicals. 9-Anthryl formate was isolated by column chromatography (silica gel, dichloromethane) without an alkaline hydrolysis of the reaction

mixture.

9-Anthryl Formate: Mp 90–91 °C; $^1\text{H NMR}$ (CDCl_3) δ =7.4–7.7 (4H, m), 7.9–8.2 (4H, m), 8.41 (1H, s), and 8.66 (1H, s); MS (70 eV) m/z (rel intensity) 222 (M^+ ; 20), 195 (16), 194 (100), 193 (18), 165 (75), and 163 (14); Found: C, 81.11; H, 4.66%; Calcd for $\text{C}_{15}\text{H}_{10}\text{O}_2$: C, 81.10; H, 4.50%.

References

- 1) The B-V reactions of ketones and aldehydes have been extensively studied, but there are only a few reports on the similar reactions of polycyclic aromatic compounds. a) Y. Ogata and Y. Sawaki, *J. Org. Chem.*, **34**, 3985 (1969). b) M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Am. Chem. Soc.*, **80**, 6393 (1958). c) Y. Ogata and Y. Sawaki, *ibid.*, **94**, 4189 (1972).
- 2) Polycyclic aromatic hydrocarbons react with carbon monoxide in the presence of aluminum chloride and hydrogen chloride to yield the corresponding aromatic aldehydes. N. N. Crounse, "Organic Reactions," John Wiley & Sons, Inc., New York (1949), Vol. 5, Chap. 6, pp. 290–300.
- 3) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., California (1972), Chap. 6, pp. 321–329.
- 4) D. Swern, "Organic Reactions," John Wiley & Sons, Inc., New York (1953), Vol. 7, Chap. 7, p. 378.

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